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CANCER MECHANISMS

Viruses and Human Cancer

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An estimated 15 percent of all human cancers worldwide may be attributed to viruses [1], representing a significant portion of the global cancer burden. Both DNA and RNA viruses have been shown to be capable of causing cancer in humans. Epstein-Barr virus, human papilloma virus, hepatitis B virus, and human herpes virus-8 are the four DNA viruses that are capable of causing the development of human cancers. Human T lymphotrophic virus type 1 and hepatitis C viruses are the two RNA viruses that contribute to human cancers.

Close study of viruses and human cancer has led to optimism for the development of new strategies for the prevention of the preceding infection that can lead to carcinogenesis. The presence of viral gene products in tumor cells that require them to maintain their unchecked proliferation also can provide important targets for directed therapies that specifically can distinguish tumor cells from normal cells. The inability of traditional cancer therapy, such as chemotherapy and radiation, to distinguish cancer cells from normal cells is a significant drawback and leads to toxicities for patients undergoing treatment. Targeted therapies directed against viral proteins or generate immune responses in order to either prevent infection or kill infected cells or cancer cells hold much promise for more effective and tolerable strategies.

Human tumor viruses

Although it is convenient to consider human tumor viruses as a discrete group of viruses, these six viruses, in fact, have very different genomes, life cycles, and represent a number of virus families. The path from viral infection to tumorgenesis is slow and inefficient; only a minority of infected individuals progress to cancer, usually years or even decades after primary infection. Virus infection also is generally not sufficient for cancer, and additional events and host factors, such as immunosuppression, somatic mutations, genetic predisposition, and exposure to carcinogens must also play a role.

Hepatitis B and C viruses

Hepatitis C virus is an enveloped RNA virus of the flavivirus family. It is capable

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†Abbreviations: EBV, Epstein-Barr virus; HHV-8, human herpesvirus; HPV, Human papillomavirus; HTLV-1, Human T lymphotropic virus type I.

of causing both acute and chronic hepatitis in humans by infecting liver cells. It is estimated that approximately 3 percent of the world's population are hepatitis C carriers [2]. Chronic infection with hepatitis C virus results in cirrhosis, which in turn can lead to primary hepatocellular carcinoma. Between 1 and 2 percent of infected patients with subsequent compensated cirrhosis will develop primary hepatocellular carcinoma per year [3]. Transmission of the virus occurs through the blood, with shared needles in intravenous drug abuse, sexual activity, and parturition being the primary routes.

The hepatitis B virus of the family hepadnaviridae is, by contrast, a DNA virus, but the features of its resulting disease share many similarities with hepatitis C virus. Hepatitis B virus also is a blood-borne pathogen that can result in acute and chronic hepatitis. Chronic hepatitis, that is infections lasting more than three months, can lead to cirrhosis and liver failure. Chronic infection also can lead to the development of hepatocellular carcinoma [4]. Hepatitis B infections is a significant global health problem with an estimated 2 billion people infected and 1.2 million deaths per year attributed to subsequent hepatitis, cirrhosis and hepatocellular carcinoma [5].

Hepatocellular carcinoma is an aggressive tumor that can occur in the setting of liver disease resulting from infections with hepatitis B and/or hepatitis C virus, although the exact mechanism of oncogenesis by these viruses is unclear. Diagnosis is usually made late in the course of liver disease and median survival ranges from six to 20 months after that time [6]. The traditional foundation of treatment is surgical, whether tumor resection or transplantation. However, nonsurgical options such as percutaneous ethanol injection, transarterial embolization, radiofrequency ablation, chemotherapy, and radiotherapy are also utilized. The choice of therapies frequently depends on the extent of disease and the amount of liver function the patient has in reserve [7,8].

Research into novel therapies have focused on the use of virally targeted and immunological strategies with an eye on preventing infection. Unfortunately, hepatitis C virus has proved to be poorly suited to vaccines because its genome possesses a very high mutation rate, especially in the hypervariable region of the genome coding for the envelope proteins allowing it to escape immune recognition and elimination by the host. There are 11 distinct genotypes and several subtypes identified.

The introduction of vaccines against hepatitis B virus in the early 1980s marked a major milestone with what might be considered the first cancer prevention vaccine, although the primary goal of this vaccine was to prevent hepatitis. Since that time, more than 110 countries have adopted a universal policy of immunizing all newborns, according to the World Health Organzation. Additionally, countries that have successfully implemented this program significantly have decreased the carrier rate and infection in their populations [9]. However, vaccine coverage is often low in many developing countries due to the cost, lack of heath care infrastructure for delivery of the vaccine, and the need for three needle injections over six months. Even in some developed nations, universal vaccination has not been implemented because of the belief that it is a limited public health problem and the expense is not justified [10,11].

New challenges for combating hepatitis B infection center around efforts to address the limitations of the current vaccine: the need for multiple injections, the presence of up to 10 percent nonresponders to the vaccine, the discovery of hepatitis B virus S gene escape mutants in infants that were infected despite an adequate response to the vaccine, and the cost for developing nations. The current multiple dosing schedule is being addressed with attempts to combine it with other required vaccines or decrease the number of doses. Oral vaccination also is being investigated as a way to obviate the need for trained personnel to administer injections. The World Health Organization estimates that from $8 to $12 billion will be needed to immunize children from the poorest countries from 2005-2010, which has prompted efforts from public and private or-

ganizations to advocate for funding to fill the need.

Medical therapy for patients infected with hepatitis B has focused on the use of interferon to reduce viral replication, which decreases the incidence of life-threatening liver complications in patients who respond to the treatment [12]. Interferon alpha treatment is effective in 20 to 30 percent of cases in inducing loss of the hepatitis B e antigen. However, the impact of interferon therapy on subsequent hepatocellular carcinoma rates is less clear [13,14]. Interferon therapy is also limited by cost and side effects.

The limitations of interferon therapy have been partly circumvented with the use of targeted antiviral agents. Lamivudine has been shown in a large multicenter randomized placebo-controlled trial to be effective in reducing both the incidence of hepatic decompensation and the risk of hepatocellular carcinoma [15]. Other antiviral agents continue to join the armamentarium; lamivudine, adefovir, entecavir, and telbivudine have been shown to be effective in hepatitis B disease. These agents are nucleotide analogues that exploit the need for the hepatitis B virus to use reverse transcriptase to replicate viral DNA. Since these agents specifically target the viral replication machinery and are given orally, they are better tolerated. However, it has been observed that long-term therapy with lamivudine can lead to the emergence of genotypic resistance mutations [16], but this does not negate the benefits of lamivudine therapy in reducing the rates of hepatocellular carcinoma [15]. The success of these therapies has reached the point where patients with advanced cirrhosis secondary to hepatitis B can be treated and transplanted without the development of hepatitis B in the transplanted liver.

Medical treatment of infection with hepatitis C has not progressed at the same speed. Pegylated interferon with ribavirin, an antiviral agent that may act as a nucleoside analogue and inhibitor of RNA dependent RNA polymerase, has been shown to be successful in eradicating infection in half of patients [17]. However, therapy is expensive and side effects are significant. Phase II trials of oral antivirals such as protease inhibitors and polymerase inhibitors are currently under way [18]. Unlike hepatitis B, treatment of hepatocellular carcinoma due to hepatitis C infection with transplantation almost always results in recurrent infection of the transplanted liver [19].

The search for targeted therapies that can block hepatitis C viral replication by selectively inhibiting viral replication has for many years been hampered by the lack of experimental infection systems, in either cell culture or animal models to test candidate therapies. The recent development of viral replicons, subgenomic RNAs that are expressed and autonomously replicate within cells, has led to the use of hepatitis C viral replicons that can replicate in human hepatoma cells lines [20] and the development of mouse models of the disease [21,22]. These advances may herald more rapid progress in the development of virally targeted therapies such as hepatitis C virus specific protease and polymerase inhibitors.

Epstein-Barr virus (EBV) and human herpesvirus 8 (HHV-8)

EBV and HHV-8 (also known as Kaposi sarcoma herpesvirus) are both herpesviruses that possess large double-stranded DNA genomes. As with all herpesviruses, they encode enzymes involved in DNA replication and repair and nucleotide biosynthesis. They also both possess the ability to establish latency in B lymphocytes and reactivate into the lytic cycle. Both also are associated with naturally occurring tumors in humans.

EBV is a ubiquitous virus that is most commonly known for being the primary agent for infectious mononucleosis. Up to 95 percent of all adults are estimated to be seropositive, and most EBV infections are subclinical. EBV also is associated with a number of malignancies: B and T cell lymphomas, Hodgkin's disease, post-transplant lymphoproliferative disease, leiomyosarcomas, and nasopharyngeal carcinomas. Of these cancers, Burkitt's lymphoma, post-transplant lymphoproliferative disease, and

leiomyosarcomas show an increased frequency in patients with immunodeficiency, suggesting a role for immunosurveillance in the suppression of malignant transformation.

The primary site of infection is the oropharyngeal cavity, and EBV is capable of infecting both B cells and epithelial cells and switching between the two [23]. The major surface glycoprotein, gp350/220, binds to the cd21 receptor on B cells. Transformation of B cells is a highly efficient process requiring a large portion of the EBV genome, which becomes circular for replication and latency. Virus will directly enter the latent gene expression state with suppression of the lytic cycle. Production of a number of latent gene products are required for immortaliztion.

Immune therapy of EBV-associated tumors has been target of research since standard therapy generally has entailed the use of multi-agent chemotherapy, radiation therapy, and surgery. This work has centered around adoptive transfer of EBV-specific cytotoxic T-cells [24,25] and shown success but must overcome obstacles such as potential graft vs. host disease and resistance due to mutation of selected EBV epitopes [26]. Vaccines capable of preventing primary EBV infection or boosting immune responses against EBV-associated tumors are under investigation. Much of the development thus far has focused on gp350/220 subunit vaccines [27], since it is one of the most abundant proteins on the virus coat and also the protein against which the human EBV neutralizing antibody response is directed [28]. Another strategy involves the use of a recombinant vaccinia viral vector to express an EBV membrane antigen [29]. A successful vaccine would have the greatest impact in regions of the world that have an especially high incidence of specific malignancies. Burkitt's lymphoma is the most common childhood malignancy in the central part of Africa where EBV and malaria are considered cofactors in its carcinogenesis and 95 percent of children are infected by age 3, compared to the United States, where infection is usually delayed until adolescence [30]. Nasopharyngeal carcinoma is relatively rare but has an exceptionally high incidence in southern China, approaching more than 20 times greater than that of most populations [31].

In 1994, HHV-8 DNA was identified in biopsies from tumors of a patient with Kaposi sarcoma [32], a relatively rare malignancy prior to the AIDS epidemic. In addition to it likely being an essential cofactor for the development of Kaposi sarcoma, HHV-8 also is believed to have a role in Castleman's disease and primary effusion lymphoma [33]. The viral genome is expressed in these tumors and encodes transforming proteins and anti-apoptotic factors. The virus is also able to enhance the proliferation of microvascular endothelial cells [34]. As with EBV, the predominant infected cell is the B lymphocyte, although here the lytic cycle is embraced rather than repressed. This may play a crucial role in the pathogenesis of Kaposis sarcoma by elaboration of viral and host cytokines promoting cell proliferation, angiogenesis, and enhancement of viral spread.

Targeted antiviral agents such as ganciclovir directed against viral DNA replication have had a dramatic affect on decreasing the incidence of Kaposi sarcoma in AIDS patients through both therapy and prophylaxis [35]. Ganciclovir is phosphorylated into a GTP analog, which acts as a competive inhibitor of viral DNA polymerase resulting in termination of viral DNA elongation. Furthermore, a G protein coupled receptor (vGPCR) has been identified as a viral oncogene in HHV-8 infected cells that can exploit cell signaling pathways to induce transformation and angiogenesis [36]. vGPCR also has been proposed as a target for novel molecular therapies because of its key role in disease progression [37]. But the therapy regimen most responsible for the decreasing incidence of Kaposi sarcoma may well be the success of highly active antiretroviral therapy (HAART) regimens targeting HIV [38], since it was the emergence of HIV that led to the increasing incidence of Kaposi sarcoma.

Human papillomavirus (HPV)

HPV are small non-enveloped DNA tumor viruses that commonly cause benign

papillomas or warts in humans. Persistent infection with high-risk subtypes of human papillomavirus (HPV) is associated with the development of cervical cancer [39]. HPV infects epithelial cells, and, after integration in host DNA, the production of oncoproteins, mainly E6 and E7, disrupts natural tumor suppressor pathways and is required for proliferation of cervical carcinoma cells [40]. HPV also is believed to play a role in other human cancers, such as head and neck tumors, skin cancers in immunosuppressed patients, and other anogenital cancers.

Cervical cancer is the second leading cause of cancer mortality in women worldwide, causing 240,000 deaths annually [41]. Of approximately 490,000 cases reported each year, more than 80 percent occur in the developing world, where effective but costly Pap smear screening programs are not in place [41]. Early precancerous changes and early cancers detected by Pap smears are effectively treated and cured with surgical therapy or ablation. In the absence of effective screening, the disease is detected late. Traditional therapeutic options for cervical cancer that have advanced beyond definitive surgical treatment are chemotherapy and radiation therapy, which are associated with many toxicities and do not offer a lasting cure.

The immune system plays an important role in the prevention of persistent HPV infection and progression of precancerous lesions. Human papillomavirus is a poor natural immunogen; as a double stranded DNA virus, there is no RNA intermediate, nor does infection cause cytolysis, allowing initiation of innate immune responses [42]. HPV mainly encodes non-secreted nucleoproteins, which are poorly cross-presented and compared to other viruses its non-structural proteins are expressed at low levels. However, genital infection with HPV is usually transient. Additionally, inadequate T cell responses may lead to failure to clear HPV-infected cells. AIDS patients, renal transplant patients receiving immunosuppressive therapy, and individuals with T cell deficiencies have increased rates of HPV persistence, anogenital lesions, and cervical cancer [43-46].

In 2006, an effective prophylactic vaccine against HPV 16 and 18 based on virus-like particles (VLP) of recombinant L1, the major capsid protein [47,48], was approved for use by the FDA based on clinical trials that demonstrated nearly 100 percent protection from persistent infection through the generation of high levels of neutralizing antibodies. Since these types are the causative agent of approximately 70 percent of cervical cancers, development of such an effective vaccine holds much promise for the prevention of cervical cancer [47]. However, the vaccine currently costs $360 for a complete course of three injections given over six months, does not provide protection against other high risk HPV types, will presumably have limited benefit to women already infected, and has an unknown duration of protection.

Because of these limitations, therapeutic vaccination is being explored to treat women already infected and accelerate the impact of prophylactic vaccination in decreasing cervical cancer incidence. Traditional therapy for early cervical cancer and precancerous lesions involves surgical excision or ablation. Therapeutic vaccination seeks to generate a population of cytoxic T cells that will recognize and kill tumor cells. Since patients with T cell deficiencies are known to be more susceptible to HPV infection and disease progression, boosting T cell responses to HPV may be crucial to a therapeutic immune strategy. In the case of cervical cancer, E6 and E7 oncoproteins are expressed in all malignancies and are not found in uninfected normal cells. Therefore, they represent ideal targets for a therapeutic immune response. A number of strategies to generate immune responses against these antigens are under investigation. Viral and bacterial vectors have been used in mouse models to generate immune responses. Vaccinia virus delivery of HPV 16 and 18 modified E6 and E7 proteins has demonstrated safety and specific immune responses in early clinical trials [49]. DNA vaccination strategies also are under active investigation, and several are in various stages of clinical trials. Vaccination with plasmid DNA encap-

sulated in biodegradable micorparticles has shown histological and immunological responses when used to treat patients with high grade cervical dysplasia [50-52].

Human T lymphotropic virus type I (HTLV-1)

HTLV-1 is a slow transforming, single stranded RNA retrovirus and is associated with adult T-cell leukemia [53]. It possesses a diploid genome similar to other retroviruses: two long terminal repeats flanking gag, pol, and env genes as well as a number of accessory genes. HTLV-1 has a worldwide distribution, with an estimated 12 to 25 million people infected. However, disease is only observed in less than 5 percent of infected individuals. It is transmitted through blood transfusions, sexual contact, and during parturition. HTLV-1 displays a special tropism for CD4 cells, which clonally proliferate in adult T cell leukemia, though how this is effected is not known.

HTLV-1 infection has a very long latency period of 20 to 30 years, but once tumor formation begins, progression is rapid. Standard chemotherapy often can bring about an initial response with a partial or complete remission; however, relapse is common, and median survival is eight months. The HTLV-1 *Tax* gene has been postulated to play an important role in tumorgenesis [54] through the activation of viral transcription and the hijacking of cellular growth and cell division machinery, but the mechanisms leading to adult T cell leukemia are not well understood. It has been suspected that HTLV-1 infection may not be sufficient to transform, and recent evidence suggests that the decreased diversity, frequency, and function of HTLV-1 specific CD8 T cells in the host may play an important part in the development of adult T-cell leukemia [55]. Therefore, targeted therapies using peptide, recombinant protein, DNA, and viral vectors with the goal of generating neutralizing antibody against HTLV-1 and multivalent cytotoxic T cell response against *Tax* are under investigation [56].

Summary

The viruses reviewed here illustrate the diverse biological pathways to malignancy and the challenges of treating the resulting diseases. Yet the presence of the viral gene products in cancer and precancerous cells present attractive targets that may be exploited in novel therapies that distinguish these cells from normal cells. Antivirals such as lamuvidine used in heptatitis B and ganciclovir for Kaposi sarcoma specifically target the viral replication machinery. Targeting cancer cells specifically would have advantages over traditional modalities such as chemotherapy and radiation, which can include significant toxicities. Cervical cancer, because it retains HPV viral oncoproteins E6 and E7 and requires their continued expression for proliferation, provides an ideal model for cytotoxic immune therapies against these known antigens.

Given the prevalence of these cancers in the developing world and the limitations of health care infrastructure, strategies for vaccine design to prevent primary infection and targeted therapies for the treatment of disease must be carefully considered in this context. Use of needles, refrigeration, multiple doses, and cost are all significant barriers to the delivery of an effective vaccine [41]. Cost, need for trained personnel and sophisticated equipment and facilities may impede global use of the most advanced targeted therapies. These challenges suggest that exploration of prophylactic strategies and development of specific, targeted therapies are both necessary to decrease this portion of the global cancer burden.

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